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GUEST EDITORIAL

How To Prevent Invasive Breast Cancer: Detect and Excise Duct Carcinoma In Situ

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Currently there is one presumed method to prevent invasive breast cancer; detect, and excise, duct carcinoma in situ (DCIS). Just as removal of colon polyps prevents invasive colon cancer [1], and the detection and local treatment of carcinoma in situ of the cervix prevents invasive carcinoma of the cervix [2], accumulating data about DCIS suggest that the detection and complete excision of DCIS of the breast can prevent many, if not most, invasive ductal cancers (IDC). However, current reviews of prevention of breast cancer fail to define excision of DCIS as the only practical, established, and current method of prevention [3]. Numerous lines of reasoning lead to this conclusion and support efforts to detect, by mammography screening, and treat, by excision, DCIS:

1. At least 75% of all patients with DCIS, when treated by local excision with histologically negative, but inadequate margins (<1 cm), have a greater than a 33% recurrence rate [4], implying that many DCIS lesions of all types are indeed persistent and progressive local neoplasms and not mere pathological curiosities.
2. After excision of DCIS of any size, grade, or rate of recurrence, 50% of all local recurrences are invasive ductal carcinoma [5–9], clearly re-emphasizing that DCIS is a significantly progressive, not inconsequential, disease in many cases.
3. Long-term follow-up of patients with low-grade small DCIS treated by biopsy only, without defined complete excision, indicates to a 30–60% incidence of IDC, some of which occur in the same site in the same breast after 30 years follow-up [10,11].
4. Median time to recurrence of low-grade DCIS is approximately 7 years [12,13], but for high-grade DCIS is about 3 years [5,6], suggesting that with continued increased recurrence rates with time, there may be a similarity of overall recurrence rates if low-grade DCIS patients are treated by inadequate excision or followed for a long enough period of time [9,12,14].
5. When excised with a ≥10 mm margin, the recurrence rate of all DCIS lesions, regardless of grade and size, is less than 10% actuarily at 12 years, substantiating the assumption that 90% or more of DCIS is unifocal in origin and can be permanently cured by adequate, but local, removal [5−7,15]. This low rate of recurrence is not further reduced by radiation therapy, indicating that the 10% of patients that fail probably result from true multifocal or multicentric origins. Indeed, many ''recurrences'' reported [8,9] are found in other quadrants of the breast after excision of DCIS and really represent multiorigin, not persistent disease.
6. Most invasive ductal carcinomas have some element of DCIS as a component of the primary lesion or scattered peripherally around the central invasive focus. Between 20% and 30% can be classified as having an extensive intraductal component (EIC+) with significant (≥25%) components of DCIS within and surrounding the invasive lesion [16]. Even IDCs that do not have an extensive intraductal component (EIC−) frequently have some DCIS in the tissue immediately adjacent to the invasive focus, although of a less prominent nature.[17] If no DCIS is seen, it is presumed that the IDC replaced or destroyed the DCIS, not that the cancer did not arise from an initial intraductal site.
7. In many cases of DCIS, there is an admixture of duct cell changes, ranging from duct hyperplasia, to atypical ductal hyperplasia, to low-grade DCIS, to advanced cellular changes that reach the level of

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high-grade DCIS of the comedo variety, to microinvasive duct carcinoma [18,19]. This spectrum of breast ductal abnormalities frequently occurs as a continuum. In general, the least cellular abnormalities occur at the periphery and the most severe abnormalities are at the center, suggesting a progression of these cellular (and genetic) changes from the center, earlier, to the periphery, later, perhaps through paracrine effects, as the neoplasm progresses and as the ductal changes spread both anatomically and temporally. Microinvasive foci seldom occur in small DCIS lesions, even when the DCIS is of high grade, but are noted in more than half of larger lesions [18]. The microinvasive foci generally do not occur at the periphery of such high-grade DCIS lesions, but within them.

8. There is an apparent progression of genetic abnormalities–both oncogenes and tumor suppressor genes–from atypical hyperplasia, to low-grade DCIS, to high-grade DCIS, to IDC, that suggests the progressive nature of oncogenesis based on a ''multi-hit'' model [20–22].
9. There is a similarity between the grade of the DCIS and the accompanying IDC [23]: high-grade DCIS is associated with high-grade IDC, while low-grade DCIS is associated with low-grade IDC [23].
10. A recent detailed three-dimensional anatomic study from Japan [24] demonstrates extensive ductal spread of DCIS from a presumed generating foci that includes invasive ductal carcinoma, illustrating the potential wide ductal spread of DCIS arising from a single small focus if not detected early enough and removed. Such extensive ductal spread of DCIS, usually of high grade, frequently develops areas of invasive ductal carcinoma over time [18].
11. The risk factors for DCIS and invasive ductal carcinoma are similar [25,26].
12. The median age of patients with DCIS is younger than those with IDC [25,26], suggesting progression from preliminary DCIS to later IDC.

These several lines of reasoning suggest that DCIS, in most cases, perhaps three-fourths or more, is a precursor lesion for later IDC and that, conversely, essentially all IDC arises from preliminary DCIS no matter how transient. In addition, this evidence implies that even low-grade DCIS followed over long time periods may lead to larger or higher-grade DCIS lesions with a high risk of invasive ductal carcinoma in the same area of the ipsilateral breast.

It can be presumed that mammographic screening in patients beginning at age 40 will lead over the subsequent years to a reduction in the incidence of invasive ductal breast cancer arising in the 6th, 7th, and 8th decades of life as a result of adequate excision of the preliminary precursor lesion, DCIS. While this has only been suggested at the present time [27], the artifactually induced increased incidence of breast cancer detected during the 1980s due to mammographic screening programs has now peaked and is leveling off or declining [27–29]. In addition, there is a decline in age-adjusted breast cancer mortality rates, both in Europe and in the United States [30–32] that seems to occur after the initiation of screening mammography programs, while also recognizing the role of therapeutic effects of adjuvant therapy. Screening results in the markedly earlier presentation of IDC with significantly smaller size and fewer node metastases, but also in the markedly more common DCIS, where incidence is still increasing. The true prevalence of DCIS however is not currently known, but eventually will be learned.

Early detection by mammography and excision of DCIS with at least a 10-mm negative margin interrupts a natural disease progression to invasive cancer; the lead time from onset of atypical ductal hyperplasia and of DCIS to development of any subsequent invasive breast cancer ranges between 10 and 20 or more years [26]. Therefore, the advantage of detecting and excising DCIS as a method to reduce the incidence and mortality of subsequent invasive ductal carcinoma will be evident only at 10–20 years, or even more, after the onset of mammographic screening programs.

There is a current controversy about the value of mammographic screening of women in their 40s, as demonstrated by the consensus panel convened by the National Institutes of Health [33]. There are those who believe that DCIS is of uncertain biological potential and represents inconsequential disease; their contention is that DCIS need not be detected or treated at an early stage, as most lesions may be innocuous, and early detection of DCIS is unnecessarily meddlesome, too expensive, and perhaps unimportant for cancer management [33]. Based on the evidence presented, there are those who think that DCIS is a precursor to IDC in many, if not most cases, which, if treated by excision after discovery by mammography, will prevent later IDC of the breast. Whether the incidental detection and excision of atypical ductal or lobular hyperplasia (ADH; ALH) is useful in prevention is uncertain because in a proportion of these lesions, progression to DCIS and later IDC may occur [34], but for the most part, such lesions are indicators of risk of later breast cancer in all breast tissue, not just in the local area excised.

In this period of intense debate of the use of genetic markers to detect susceptible populations of women for prevention techniques that are as yet unproven [35], we may lose sight of the fact that a technique is available today that will abort the development of a large proportion, if not the majority, of invasive breast cancers. Routine mammographic screening should be applied to women beginning at the age of 40 and at least yearly subsequent intervals. As a nation, we should commit our-

selves to universal mammographic screening of appropriately aged women, to achieve a sharp reduction in the size and aggressiveness of IDC, but also to prevent IDC of the breast by detecting and excising DCIS. Better understanding of the biologic behavior of DCIS [36] is rapidly accumulating and may help to support these arguments regarding prevention.

This article attempts to reframe one aspect of the debate regarding mammographic screening while recognizing the major public health benefits of reducing the size [37] and biological potential [38,39] of invasive breast cancer. Detection and excision of preinvasive lesions also acknowledges its important potential role in preventing the majority of IDCs over the decades ahead.

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